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(54) Title: NOVEL RECEPTOR

(57) Abstract

The invention provides isolated polynucleotide molecules encoding a novel G–protein–coupled receptor (designated TSR32). These isolated polynucleotide molecules can be used to express the receptor in cells which can then be used to screen compounds for agonist and antagonist activity.

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NOVEL RECEPTOR

Field of the Invention:-

The present invention relates to isolated polynucleotide molecules which encode a novel seven-transmembrane G-protein-coupled receptor designated TSR32. In addition, the present invention relates to the use of these molecules in the production of TSR32 receptors using recombinant technology and to methods of screening compounds for agonists and/or antagonists of the TSR32 receptor.

Background of the Invention:-

Proteins with seven-transmembrane (7TM) segments define a superfamily of receptors with a common structure comprising an extracellular N-terminus, three extramembranous loops on either side of the plasma membrane, and a cytoplasmic C-terminus. The majority of such proteins function as cell-surface receptors for a variety of ligands, including small molecules, peptides, hormones, ions, and external sensory stimuli such as odorants (Watson, S. and Arkinstall, S., The G-protein Linked Receptor Facts Book, Academic Press, London, 1994). One family within the 7TM superfamily is known as the secretin receptor family and comprises member receptors with specificity for secretin, calcitonin, glucagon, glucagon-like peptide 1, parathyroid hormone, parathyroid-related peptide, corticotropin-releasing factor (CRF), growth hormone-releasing hormone (GHRH), gastric inhibitory polypeptide, pituitary adenylate-cyclase-activating polypeptide (PACAP), vasoactive intestinal peptides (VIP) and insect diuretic hormone (DHR).

The present inventor has now identified a further member receptor of the secretin receptor family. This receptor, designated TSR32, appears to be expressed in a large variety of tissue types including heart, kidney, lung and brain with highest levels in the thyroid gland. Since agonists and/or antagonists for this receptor may have commercial value, for example as regulators of important thyroid functions in growth, development and metabolic activity, the ability to produce TSR32 receptors by recombinant DNA technology would be advantageous.

RNSDOCID: <WO 9915551A1_I_>

Disclosure of the Invention:-

Thus, in a first aspect, the present invention provides an isolated polynucleotide molecule encoding a G-protein-coupled receptor, designated TSR32, which is characterised by the N-terminal amino acid sequence:

MTPQSLLQTT (SEQ ID NO: 1),

or a functionally equivalent fragment of said receptor.

Preferably, the polynucleotide molecule encodes a human TSR32 receptor of about 693 amino acids.

More preferably, the isolated polynucleotide molecule encodes a human TSR32 receptor comprising an amino acid sequence substantially corresponding to that shown as SEQ ID NO: 2 or a functionally equivalent fragment thereof.

The nucleotide sequence of a polynucleotide molecule in accordance with the first aspect, may comprise a nucleotide sequence substantially corresponding to or, showing at least 75% (preferably, at least 90% or, even more preferably, at least 95%) sequence identity to that shown as SEQ ID NO: 3 or SEQ ID NO: 4 or any portion thereof encoding a functionally equivalent TSR32 receptor fragment.

The polynucleotide molecule may be incorporated into plasmids or expression vectors (including viral vectors), which may then be introduced into suitable host cells (e.g. bacterial, yeast, insect and mammalian host cells). Such host cells may be used to express the TSR32 receptor encoded by the isolated polynucleotide molecule.

Accordingly, in a second aspect, the present invention provides a host cell transformed with the polynucleotide molecule of the first aspect.

In a third aspect, the present invention provides a method of producing TSR32 receptors or functionally equivalent fragments thereof, comprising culturing the host cell of the second aspect under conditions enabling the expression of the polynucleotide molecule and, optionally, recovering the TSR32 receptor or fragments thereof.

Preferably, the host cell is mammalian or of insect origin. Where the cell is mammalian, it is presently preferred that it be a Chinese hamster ovary (CHO) cell or a human embryonic kidney (HEK) 293 cell. Where the cell is of insect origin, it is presently preferred that it be an insect Sf9 cell.

In a preferred embodiment, the TSR32 receptor or fragments thereof are expressed onto the surface of the host cells.

The polynucleotide molecules of the present invention represent a new subfamily of the secretin receptor family which may be of interest both clinically and commercially as it is expressed in many tissue types and may therefore be involved in a wide variety of systems.

By using the polynucleotide molecules of the present invention it is possible to obtain TSR32 receptor protein or functionally equivalent fragments thereof in a substantially pure form.

Accordingly, in a fourth aspect, the present invention provides a G-protein-coupled receptor, designated TSR32, which is characterised by the N-terminal amino acid sequence:

MTPQSLLQTT (SEQ ID NO: 1),

or a functionally equivalent fragment thereof, in a substantially pure form.

Preferably, the purified TSR32 receptor has an amino acid sequence substantially corresponding to that shown as SEQ ID NO: 2.

In a fifth aspect, the present invention provides an antibody or antibody fragment capable of specifically binding to a TSR32 receptor according to the fourth aspect.

The antibody may be monoclonal or polyclonal, however, it is presently preferred that the antibody is a monoclonal antibody. Suitable antibody fragments include Fab, $(F(ab')_2$ and scFv.

In a sixth aspect, the present invention provides a non-human animal transformed with a polynucleotide molecule according to the first aspect of the present invention.

In a seventh aspect, the present invention provides a method for detecting agonist and/or antagonist compounds of the TSR32 receptor, comprising contacting a TSR32 receptor, functionally equivalent fragment thereof or a host cell transformed with and expressing the polynucleotide molecule of the first aspect, with a test compound under conditions enabling the activation of the TSR32 receptor or functionally equivalent fragment thereof, and detecting an increase or decrease in the activity of the TSR32 receptor or functionally equivalent fragment thereof.

An increase or decrease in activity of the receptor or functionally equivalent fragment thereof may be detected by measuring changes in CAMP production, CA^{2+} levels or IP3 turnover after activating the receptor or fragment thereof with specific agonists or antagonists.

In a further aspect, the present invention provides an oligonucleotide or polynucleotide probe comprising a nucleotide sequence of 10 or more nucleotides, the probe comprising a nucleotide sequence such that the probe specifically hybridises to the polynucleotide molecule of the first aspect under high stringency conditions (Sambrook *et al., Molecular Cloning: a laboratory manual*, Second Edition, Cold Spring Harbor Laboratory Press).

Preferably the probe is labelled.

In a still further aspect, the present invention provides an antisense polynucleotide molecule comprising a nucleotide sequence capable of specifically hybridising to an mRNA molecule which encodes a TSR32 receptor so as to prevent translation of the mRNA molecule.

Such antisense polynucleotide molecules may include a ribozyme region to catalytically inactivate mRNA to which it is hybridized.

The polynucleotide molecule of the first aspect of the invention may be a dominant negative mutant which encodes a gene product causing an altered phenotype by, for example, reducing or eliminating the activity of endogenous TSR32 receptors.

The term "substantially corresponding" as used herein in relation to amino acid sequences is intended to encompass minor variations in the amino acid sequences which do not result in a decrease in the biological activity of the TSR32 receptor. These variations may include conservative amino acids substitutions. The substitutions envisaged are:-

G, A, V, I, L, M; D, E; N, Q; S, T; K, R, H; F. Y, W, H; and

P, Nα-alkalamino acids.

The term "substantially corresponding" as used herein in relation to nucleotide sequences is intended to encompass minor variations in the nucleotide sequence which due to degeneracy in the DNA code do not result in a change in the encoded protein. Further, this term is intended to encompass other minor variations in the sequence which may be required to enhance expression in a particular system but in which the variations do not result in a decrease and biological activity of the encoded protein.

The term "functionally equivalent fragment/s" as used herein is intended to refer to fragments of the TSR32 receptor that exhibit binding specificity and activity that is substantially equivalent to the full length receptor from which it/they is/are derived.

The terms "comprise", "comprises" and "comprising" as used throughout the specification are intended to refer to the inclusion of a stated step, component or feature or group of steps, components or features with or without the inclusion of a further step, component or feature or group of steps, components or features.

Brief description of the figures:-

Figure 1 provides the nucleotide sequence of a cDNA encoding the human TSR32 receptor and includes the predicted amino acid sequence.

Figure 2 provides a sequence alignment of the amino acid sequences of the human TSR32 receptor and the human epididymis-specific HE6 receptor (Osterhoff, C., *DNA and Cell Biology*, Vol. 16 No. 4, 1997).

Example:-

Degenerative oligonucleotides corresponding to conserved regions within the human Glucagon-like peptide receptor (GLP1) family were used to amplify specific DNA sequences from a variety of cDNA library DNA's. Library DNA from human hypothalamus and heart yielded fragments of the expected size. These fragments were subcloned and sequenced. One fragment, 456bp long, revealed a novel 7TM receptor sequence distantly related to the secretin receptor family. Screening a human heart cDNA library (Stratagene) using this fragment under high stringency conditions identified two positive hybridising clones, 1 and 2.9kb in size, respectively. The larger clone contains an open reading frame of 2079 nucleotides encoding a 693 amino acid long protein (designated TSR32). The nucleotide and putative amino acid sequence is provided at Figure 1.

A search of the EMBL/GenBank database revealed low but significant sequence similarities to the secretin receptor family of TM7 receptors. The sequence similarity to the above receptor sequences is only about 25% identity and also limited to the transmembrane region. However, the highest overall sequence similarity was found to four other G-protein coupled receptor subtypes, the human epididymis-specific HE6 (31% identity), the human lymphocyte antigen CD97 (33% identity), the orphan human receptor EMR1 (27% identity), the insect DHR (26% identity) and the rat latrophilin-

related protein 1 precursor (35% identity) all of which share a large extracellular domain with numerous putative O- and N-glycosylation sites. Except for DHR, in all of the receptors there is a cysteine motif preceding the first transmembrane domain. Further, in contrast to the CD97 and EMR1 receptors, TSR32 does not contain any EGF-domains or calcium binding sites in the extracellular domain.

Interestingly, at the gene level the exon/intron organisation of the TSR32-encoding cDNA, at least within the region encoding the transmembrane domain, is most similar to the gene structure of the PACAP receptor family, with fewer but identical exon/intron borders.

Northern analysis indicates a low level of expression of the receptor mRNA in a large variety of tissues including kidney, lung, cerebellum and heart. The highest level of mRNA however, was found in the thyroid gland. This expression pattern of the receptor mRNA indicates that TSR32 has important functions in metabolic regulations throughout the body via the thyroid gland.

The gene for TSR32 has been mapped to human chromosome 16q31 by *in situ* hybridisation and this localisation was confirmed by radiation hybrid analysis. An autosomal recessive disorder (Bardet Biedl Syndrome; Kwitek-Black, A.E. *et al., Nature Genetics* 5: 392-396, 1993) has also been linked to this region. Features of this syndrome include obesity, retinal degeneration, hypogonadism and mental retardation. The expression of TSR32 examined by *in situ* hybridisation and Northern analysis overlaps strongly with the tissues affected in the Bardet Biedl Syndrome making TSR32 a good candidate for this locus.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Sequence listings:-

Applicant: Garvan Institute of Medical Research

Title of Invention: Novel receptor

Number of SEQ ID Nos: 4

SEQ ID NO: 1
Length: 10
Type PRT
Organism: Homo sapiens

Sequence: 1
Met Thr Pro Gln Ser Leu Leu Gln Thr Thr
1 5 10

SEQ ID NO: 2
Length 693
Type PRT
Organism: Homo sapiens

Sequence: 2
Met Thr Pro Gln Ser Leu Leu Gln Thr Thr Leu Phe Leu Leu Ser Leu
1 5 10 15

Leu Phe Leu Val Gln Gly Ala His Gly Arg Gly His Arg Glu Asp Phe
20 25 30

Arg Phe Cys Ser Gln Arg Asn Gln Thr His Arg Ser Ser Leu His Tyr
35 40 45

Lys Pro Thr Pro Asp Leu Arg Ile Ser Ile Glu Asn Ser Glu Glu Ala
50 55 60

Leu Thr Val His Ala Pro Phe Pro Ala Ala His Pro Ala Ser Arg Ser
65 70 75 80

Phe Pro Asp Pro Arg Gly Leu Tyr His Phe Cys Leu Tyr Trp Asn Arg
85 90 95

His Ala Gly Arg Leu His Leu Leu Tyr Gly Lys Arg Asp Phe Leu Leu
100 105 110

Ser Asp Lys Ala Ser Ser Leu Leu Cys Phe Gln His Gln Glu Glu Ser
115 120 125

Leu Ala Gln Gly Pro Pro Leu Leu Ala Thr Ser Val Thr Ser Trp Trp
130 135 140

Ser Pro Gln Asn Ile Ser Leu Pro Ser Ala Ala Ser Phe Thr Phe Ser

145 150 155 160

Phe His Ser Pro Pro His Thr Ala Ala His Asn Ala Ser Val Asp Met
165 170 175

Cys Glu Leu Lys Arg Asp Leu Gln Leu Leu Ser Gln Phe Leu Lys His
180 185 190

Pro Gln Lys Ala Ser Arg Arg Pro Ser Ala Ala Pro Ala Ser Gln Gln
195 200 205

Leu Gln Ser Leu Glu Ser Lys Leu Thr Ser Val Arg Phe Met Gly Asp
210 215 220

Met Val Ser Phe Glu Glu Asp Arg Ile Asn Ala Thr Val Trp Lys Leu
225 230 235 240

Gln Pro Thr Ala Gly Leu Gln Asp Leu His Ile His Ser Arg Gln Glu
245 250 255

Glu Glu Gln Ser Glu Ile Met Glu Tyr Ser Val Leu Leu Pro Arg Thr
260 265 270

Leu Phe Gln Arg Thr Lys Gly Arg Ser Gly Glu Ala Glu Lys Arg Leu
275 280 285

Leu Leu Val Asp Phe Ser Ser Gln Ala Leu Phe Gln Asp Lys Asn Ser
290 295 300

Ser Gln Val Leu Gly Glu Lys Val Leu Gly Ile Val Val Gln Asn Thr
305 310 315 320

Lys Val Ala Asn Leu Thr Glu Pro Val Val Leu Thr Phe Gln His Gln
325 330 335

Leu Gln Pro Lys Asn Val Thr Leu Gln Cys Val Phe Trp Val Glu Asp
340 345 350

Pro Thr Leu Ser Ser Pro Gly His Trp Ser Ser Ala Gly Cys Glu Thr
355 360 365

Val Arg Arg Glu Thr Gln Thr Ser Cys Phe Cys Asn His Leu Thr Tyr
370 375 380

Phe Ala Val Leu Met Val Ser Ser Val Glu Val Asp Ala Val His Lys
385 390 395 400

His Tyr Leu Ser Leu Leu Ser Tyr Val Gly Cys Val Val Ser Ala Leu
405 410 415

Ala Cys Leu Val Thr Ile Ala Ala Tyr Leu Cys Ser Arg Val Pro Leu
420 425 430

Pro Cys Arg Arg Lys Pro Arg Asp Tyr Thr Ile Lys Val His Met Asn
435 440 445

Leu Leu Leu Ala Val Phe Leu Leu Asp Thr Ser Phe Leu Leu Ser Glu
450 455 460

Pro Val Ala Leu Thr Gly Ser Glu Ala Gly Cys Arg Ala Ser Ala Ile
465 470 475 480

Phe Leu His Phe Ser Leu Leu Thr Cys Leu Ser Trp Met Gly Leu Glu
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Gly Tyr Asn Leu Tyr Arg Leu Val Val Glu Val Phe Gly Thr Tyr Val
500 505 510

Pro Gly Tyr Leu Leu Lys Leu Ser Ala Met Gly Trp Gly Phe Pro Ile
515 520 525

Phe Leu Val Thr Leu Val Ala Leu Val Asp Val Asp Asn Tyr Gly Pro
530 535 540

Ile Ile Leu Ala Val His Arg Thr Pro Glu Gly Val Ile Tyr Pro Ser
545 550 555 560

Met Cys Trp Ile Arg Asp Ser Leu Val Ser Tyr Ile Thr Asn Leu Gly
565 570 575

Leu Phe Ser Leu Val Phe Leu Phe Asn Met Ala Met Leu Ala Thr Met
580 585 590

Val Val Gln Ile Leu Arg Leu Arg Pro His Thr Gln Lys Trp Ser His
595 600 605

Val Leu Thr Leu Leu Gly Leu Ser Leu Val Leu Gly Leu Pro Trp Ala
610 615 620

Leu Ile Phe Phe Ser Phe Ala Ser Gly Thr Phe Gln Leu Val Val Leu
625 630 635 640

Tyr Leu Phe Ser Ile Ile Thr Ser Phe Gln Gly Phe Leu Ile Phe Ile
645 650 655

Trp Tyr Trp Ser Met Arg Leu Gln Ala Arg Gly Gly Pro Ser Pro Leu
660 665 670

Lys Ser Asn Ser Asp Cys Ala Arg Leu Pro Ile Ser Ser Gly Ser Thr
675 680 685

Ser Ser Ser Arg Ile
690

SEQ ID NO: 3
Length 2082
Type DNA
Organism: Homo sapiens

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SEQ ID NO: 4
Length 2834
Type DNA
Organism: Homo sapiens

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tcgggcagca cctcgtccag ccgcatctag gcctccagcc cacctgccca tgtgatgaag 2280
cagagatgcg gcctcgtcgc acactgcctg tggcccccga gccaggccca gccccaggcc 2340
agtcagccgc agactttgga aagcccaacg accatggaga gatgggccgt tgccatggtg 2400
gacggactcc cggggctggg gcttttgaat tggccttggg gactactcgg ctctcactca 2460
gctcccacgg gactcagaag tgcgccgcca tgctgcctag ggtactgtcc ccacatctgt 2520
cccaacccag ctggaggcct ggtctctcct tacaacccct gggcccagcc tcattgctgg 2580
gggccaggcc ttggatcttg agggtctggc acatccttaa tcctgtgccc ctgcctggga 2640
cagaaatgtg gctccagttg ctctgtctct cgtggtcacc ctgagggcac tctgcatcct 2700
ctgtcatttt aacctcaggt ggcacccagg gcgaatgggg cccagggcag accttcaggg 2760
ccagagccct ggcggaggag aggccctttg ccaggagcac agcagcagct cgcctacctc 2820
tgagcccgga attc 2834

Claims:

1. An isolated polynucleotide molecule encoding a G-protein-coupled receptor which is characterised by the N-terminal amino acid sequence:
MTPQSLLQTT (SEQ ID NO: 1),
or a functionally equivalent fragment of said receptor.

2. A polynucleotide molecule according to claim 1, wherein said polynucleotide molecule encodes a G-protein-coupled receptor of human origin of about 693 amino acids in length.

3. A polynucleotide molecule according to claim 2, wherein the polynucleotide molecule encodes a G-protein-coupled receptor comprising an amino acid sequence substantially corresponding to that shown as SEQ ID NO: 2.

4. An isolated polynucleotide molecule encoding a G-protein-coupled receptor, wherein the polynucleotide molecule comprises a nucleotide sequence showing at least 75% sequence identity to that shown as SEQ ID NO: 3 or SEQ ID NO: 4 or any portion thereof encoding a functionally equivalent receptor fragment.

5. A polynucleotide molecule according to claim 4, wherein the polynucleotide molecule comprises a nucleotide sequence showing at least 90% sequence identity to that shown as SEQ ID NO: 3 or SEQ ID NO: 4 or any portion thereof encoding a functionally equivalent receptor fragment.

6. A polynucleotide molecule according to claim 5, wherein the polynucleotide molecule comprises a nucleotide sequence showing at least 95% sequence identity to that shown as SEQ ID NO: 3 or SEQ ID NO: 4 or any portion thereof encoding a functionally equivalent receptor fragment.

7. A plasmid or expression vector including a polynucleotide molecule according to any one of the preceding claims.

8. A host cell transformed with a polynucleotide molecule according to any one of claims 1 to 6.

9. A host cell according to claim 8, wherein the cell is a mammalian or insect cell.

10. A host cell according to claim 9, wherein the cell is a Chinese hamster ovary (CHO) cell, human embryonic kidney (HEK) 293 cell or an insect Sf9 cell.

11. A host cell according to any one of claims 8 to 10 wherein the cell expresses the G-protein-coupled receptor or functionally equivalent fragment thereof onto the cell's surface.

12. A G-protein-coupled receptor which is characterised by the N-terminal amino acid sequence:

MTPQSLLQTT (SEQ ID NO: 1),

or a functionally equivalent fragment of said receptor, in a substantially pure form.

13. A receptor according to claim 12, wherein said receptor is a human receptor of about 693 amino acids.

14. A receptor according to claim 13, wherein the receptor has an amino acid sequence substantially corresponding to that shown as SEQ ID NO: 2.

15. An antibody or fragment thereof which specifically binds to a G-protein-coupled receptor according to any one of claims 12 to 14.

16. A non-human animal transformed with a polynucleotide molecule according to any one of claims 1 to 6.

17. A method for detecting agonist or antagonist agents of a G-protein-coupled receptor comprising, contacting a G-protein-coupled receptor according to any one of claims 12 to 14 or a host cell transformed with and expressing a DNA molecule according to any one of claims 1 to 6, with a test

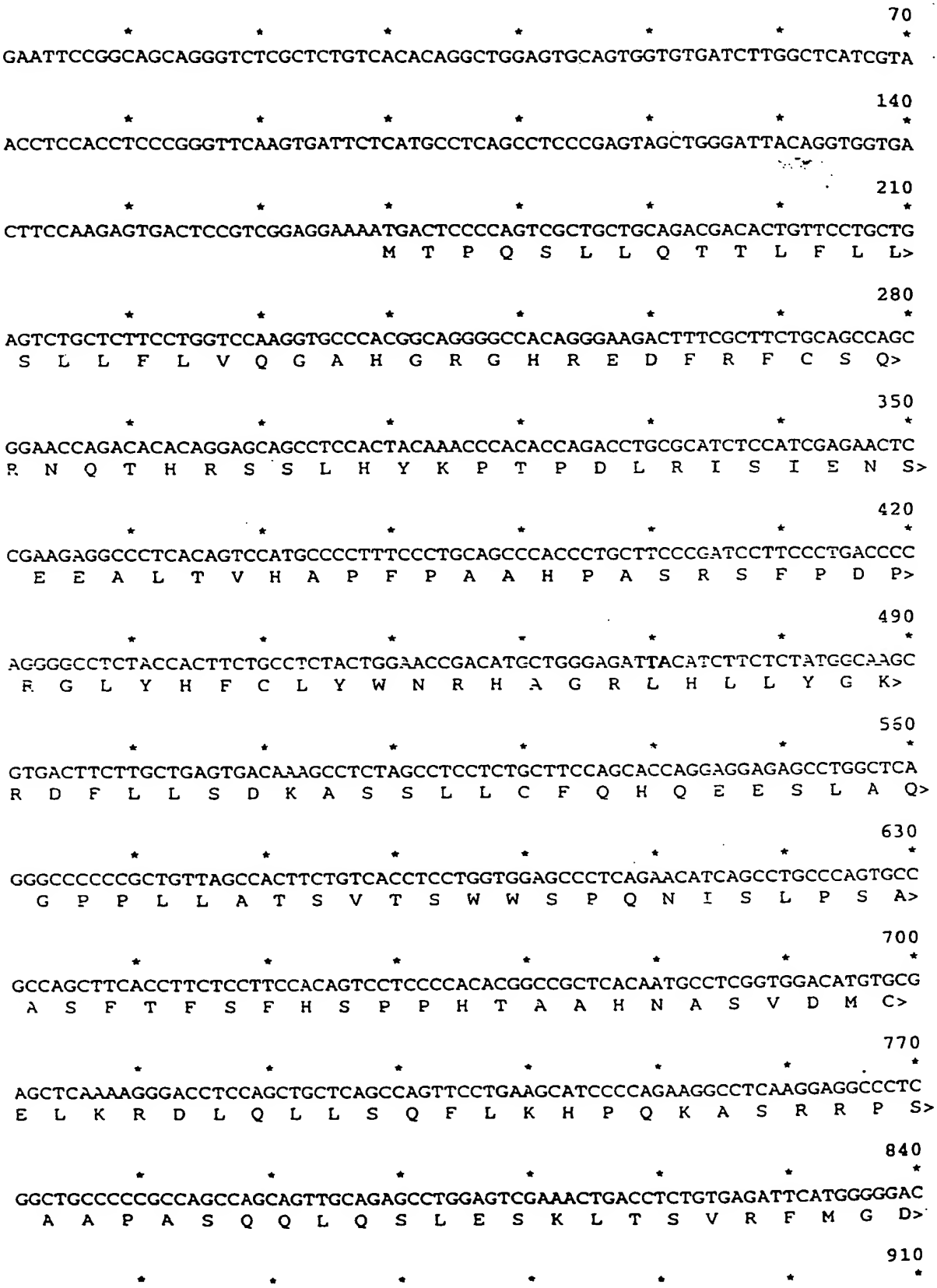
agent under conditions enabling the activation of the receptor, and detecting an increase or decrease in the receptor activity.

18. An oligonucleotide or polynucleotide probe comprising a nucleotide sequence of 10 or more nucleotides, the probe comprising a nucleotide sequence such that the probe specifically hybridises to the polynucleotide molecule of any one of claims 1 to 6 under high stringency conditions.

19. An antisense polynucleotide molecule comprising a nucleotide sequence capable of specifically hybridising to an mRNA molecule which encodes a G-protein-coupled receptor encoded by the polynucleotide molecule of any one of claims 1 to 6, so as to prevent translation of the mRNA molecule.

20. A method of producing G-protein-coupled receptors or functionally equivalent fragments thereof according to any one of claims 12 to 14, comprising culturing a host cell according to any one of claims 8 to 11 under conditions enabling the expression of the polynucleotide molecule and optionally recovering the receptors or functionally equivalent fragments thereof.

FIGURE 1 1/5


70
GAATTCCGGCAGCAGGGTCTCGCTCTGTCACACAGGCTGGAGTGCAGTGGTGTGATCTTGGCTCATCGTA
140
ACCTCCACCTCCCGGGTTCAAGTGATTCTCATGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGTGGTGA
210
CTTCCAAGAGTGACTCCGTCGGAGGAAAATGACTCCCCAGTCGCTGCTGCAGACGACACTGTTCCTGCTG
M T P Q S L L Q T T L F L L>
280
AGTCTGCTCTTCCTGGTCCAAGGTGCCCACGGCAGGGGCCACAGGGAAGACTTTCGCTTCTGCAGCCAGC
S L L F L V Q G A H G R G H R E D F R F C S Q>
350
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R N Q T H R S S L H Y K P T P D L R I S I E N S>
420
CGAAGAGGCCCTCACAGTCCATGCCCCTTTCCCTGCAGCCCACCCTGCTTCCCGATCCTTCCCTGACCCC
E E A L T V H A P F P A A H P A S R S F P D P>
490
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R G L Y H F C L Y W N R H A G R L H L L Y G K>
560
GTGACTTCTTGCTGAGTGACAAAGCCTCTAGCCTCCTCTGCTTCCAGCACCAGGAGGAGAGCCTGGCTCA
R D F L L S D K A S S L L C F Q H Q E E S L A Q>
630
GGGCCCCCCGCTGTTAGCCACTTCTGTCACCTCCTGGTGGAGCCCTCAGAACATCAGCCTGCCCAGTGCC
G P P L L A T S V T S W W S P Q N I S L P S A>
700
GCCAGCTTCACCTTCTCCTTCCACAGTCCTCCCCACACGGCCGCTCACAATGCCTCGGTGGACATGTGCG
A S F T F S F H S P P H T A A H N A S V D M C>
770
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E L K R D L Q L L S Q F L K H P Q K A S R R P S>
840
GGCTGCCCCCGCCAGCCAGCAGTTGCAGAGCCTGGAGTCGAAACTGACCTCTGTGAGATTCATGGGGGAC
A A P A S Q Q L Q S L E S K L T S V R F M G D>
910

```
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 M  V  S  F  E  E  D  R  I  N  A  T  V  W  K  L  Q  P  T  A  G  L  Q>

                                                                      980
        *        *        *        *        *        *        *
ACCTGCACATCCACTCCCGGCAGGAGGAGGAGCAGAGCGAGATCATGGAGTACTCGGTGCTGCTGCCTCG
D  L  H  I  H  S  R  Q  E  E  E  Q  S  E  I  M  E  Y  S  V  L  L  P  R>

                                                                     1050
        *        *        *        *        *        *        *
AACACTCTTCCAGAGGACGAAAGGCCGGAGCGGGGAGGCTGAGAAGAGACTCCTCCTGGTGGACTTCAGC
  T  L  F  Q  R  T  K  G  R  S  G  E  A  E  K  R  L  L  L  V  D  F  S>

                                                                     1120
        *        *        *        *        *        *        *
AGCCAAGCCCTGTTCCAGGACAAGAATTCCAGCCAAGTCCTGGGTGAGAAGGTCTTGGGGATTGTGGTAC
 S  Q  A  L  F  Q  D  K  N  S  S  Q  V  L  G  E  K  V  L  G  I  V  V>

                                                                     1190
        *        *        *        *        *        *        *
AGAACACCAAAGTAGCCAACCTCACGGAGCCCGTGGTGCTCACTTTCCAGCACCAGCTACAGCCGAAGAA
Q  N  T  K  V  A  N  L  T  E  P  V  V  L  T  F  Q  H  Q  L  Q  P  K  N>

                                                                     1260
        *        *        *        *        *        *        *
TGTGACTCTGCAATGTGTGTTCTGGGTTGAAGACCCCACATTGAGCAGCCCGGGGCATTGGAGCAGTGCT
  V  T  L  Q  C  V  F  W  V  E  D  P  T  L  S  S  P  G  H  W  S  S  A>

                                                                     1330
        *        *        *        *        *        *        *
GGGTGTGAGACCGTCAGGAGAGAAACCCAAACATCCTGCTTCTGCAACCACTTGACCTACTTTGCAGTGC
 G  C  E  T  V  R  R  E  T  Q  T  S  C  F  C  N  H  L  T  Y  F  A  V>

                                                                     1400
        *        *        *        *        *        *        *
TGATGGTCTCCTCGGTGGAGGTGGACGCCGTGCACAAGCACTACCTGAGCCTCCTCTCCTACGTGGGCTG
L  M  V  S  S  V  E  V  D  A  V  H  K  H  Y  L  S  L  L  S  Y  V  G  C>

                                                                     1470
        *        *        *        *        *        *        *
TGTCGTCTCTGCCCTGGCCTGCCTTGTCACCATTGCCGCCTACCTCTGCTCCAGGGTGCCCCTGCCGTGC
  V  V  S  A  L  A  C  L  V  T  I  A  A  Y  L  C  S  R  V  P  L  P  C>

                                                                     1540
        *        *        *        *        *        *        *
AGGAGGAAACCTCGGGACTACACCATCAAGGTGCACATGAACCTGCTGCTGGCCGTCTTCCTGCTGGACA
 R  R  K  P  R  D  Y  T  I  K  V  H  M  N  L  L  L  A  V  F  L  L  D>

                                                                     1610
        *        *        *        *        *        *        *
CGAGCTTCCTGCTCAGCGAGCCGGTGGCCCTGACAGGCTCTGAGGCTGGCTGCCGAGCCAGTGCCATCTT
T  S  F  L  L  S  E  P  V  A  L  T  G  S  E  A  G  C  R  A  S  A  I  F>

                                                                     1680
        *        *        *        *        *        *        *
CCTGCACTTCTCCCTGCTCACCTGCCTTTCCTGGATGGGCCTCGAGGGGTACAACCTCTACCGACTCGTG
  L  H  F  S  L  L  T  C  L  S  W  M  G  L  E  G  Y  N  L  Y  R  L  V>

                                                                     1750
        *        *        *        *        *        *        *
GTGGAGGTCTTTGGCACCTATGTCCCTGGCTACCTACTCAAGCTGAGCGCCATGGGCTGGGGCTTCCCCA
 V  E  V  F  G  T  Y  V  P  G  Y  L  L  K  L  S  A  M  G  W  G  F  P>
```

```
                                                                    1820
          *         *         *         *         *         *         *
TCTTTCTGGTGACGCTGGTGGCCCTGGTGGATGTGGACAACTATGGCCCCATCATCTTGGCTGTGCATAG
I  F  L  V  T  L  V  A  L  V  D  V  D  N  Y  G  P  I  I  L  A  V  H  R>

                                                                    1890
          *         *         *         *         *         *         *
GACTCCAGAGGGCGTCATCTACCCTTCCATGTGCTGGATCCGGGACTCCCTGGTCAGCTACATCACCAAC
   T  P  E  G  V  I  Y  P  S  M  C  W  I  R  D  S  L  V  S  Y  I  T  N>

                                                                    1960
          *         *         *         *         *         *         *
CTGGGCCTCTTCAGCCTGGTGTTTCTGTTCAACATGGCCATGCTAGCCACCATGGTGGTGCAGATCCTGC
  L  G  L  F  S  L  V  F  L  F  N  M  A  M  L  A  T  M  V  V  Q  I  L>

                                                                    2030
          *         *         *         *         *         *         *
GGCTGCGCCCCCACACCCAAAAGTGGTCACATGTGCTGACACTGCTGGGCCTCAGCCTGGTCCTTGGCCT
R  L  R  P  H  T  Q  K  W  S  H  V  L  T  L  L  G  L  S  L  V  L  G  L>

                                                                    2100
          *         *         *         *         *         *         *
GCCCTGGGCCTTGATCTTCTTCTCCTTTGCTTCTGGCACCTTCCAGCTTGTCGTCCTCTACCTTTTCAGC
   P  W  A  L  I  F  F  S  F  A  S  G  T  F  Q  L  V  V  L  Y  L  F  S>

                                                                    2170
          *         *         *         *         *         *         *
ATCATCACCTCCTTCCAAGGCTTCCTCATCTTCATCTGGTACTGGTCCATGCGGCTGCAGGCCCGGGGTG
  I  I  T  S  F  Q  G  F  L  I  F  I  W  Y  W  S  M  R  L  Q  A  R  G>

                                                                    2240
          *         *         *         *         *         *         *
GCCCCTCCCCTCTGAAGAGCAACTCAGACTGCGCCAGGCTCCCCATCAGCTCGGGCAGCACCTCGTCCAG
G  P  S  P  L  K  S  N  S  D  C  A  R  L  P  I  S  S  G  S  T  S  S  S>

                                                                    2310
          *         *         *         *         *         *         *
CCGCATCTAGGCCTCCAGCCCACCTGCCCATGTGATGAAGCAGAGATGCGGCCTCGTCGCACACTGCCTG
   R  I>

                                                                    2380
          *         *         *         *         *         *         *
TGGCCCCCGAGCCAGGCCCAGCCCCAGGCCAGTCAGCCGCAGACTTTGGAAAGCCCAACGACCATGGAGA

                                                                    2450
          *         *         *         *         *         *         *
GATGGGCCGTTGCCATGGTGGACGGACTCCCGGGGCTGGGGCTTTTGAATTGGCCTTGGGGACTACTCGG

                                                                    2520
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CTCTCACTCAGCTCCCACGGGACTCAGAAGTGCGCCGCCATGCTGCCTAGGGTACTGTCCCCACATCTGT

                                                                    2590
          *         *         *         *         *         *         *
CCCAACCCAGCTGGAGGCCTGGTCTCTCCTTACAACCCCTGGGCCCAGCCTCATTGCTGGGGGCCAGGCC

                                                                    2660
          *         *         *         *         *         *         *
TTGGATCTTGAGGGTCTGGCACATCCTTAATCCTGTGCCCCTGCCTGGGACAGAAATGTGGCTCCAGTTG
```

CTCTGTCTCTCGTGGTCACCCTGAGGGCACTCTGCATCCTCTGTCATTTTAACCTCAGGTGGCACCCAGG

2800

GCGAATGGGGCCCAGGGCAGACCTTCAGGGCCAGAGCCCTGGCGGAGGAGAGGCCCTTTGCCAGGAGCAC

AGCAGCAGCTCGCCTACCTCTGAGCCCGGAATTC

FIGURE 2


```
hU32p   1    MVFSVRQCGHVGRTEEVLLTFKIFLVIICLHVVLVTSLEEDTDNSSLSPPPAKLSVVSFAPSSNEVETT
HE6p    1    MVFSVRQCGHVGRTEEVLLTFKIFLVIICLHVVLVTSLEEDTDNSSLSPPPAKLSVVSFAPSSNEVETT
hU32p   1    SLNDVTLSLLPSNETEKTKITIVKTFNASGVKPQRNICNLSSICNDSAFFRGEIMFQYDKESTVPQNOH
HE6p   70    SLNDVTLSLLPSNETEKTKITIVKTFNASGVKPQRNICNLSSICNDSAFFRGEIMFQYDKESTVPQNOH
hU32p   1    ITNGTLTGVLSLSELKRSELNKTLQTLSETYFIMCATAEAQSTLNCTFTIKLNNTMNACAAIAALERVK
HE6p  139    ITNGTLTGVLSLSELKRSELNKTLQTLSETYFIMCATAEAQSTLNCTFTIKLNNTMNACAAIAALERVK
hU32p   1    ------------MTPQSLLQTTLFLSLLFLVQGAHGRGHREDFRFCSQRNQTHRSSLHYKPTPDLRIS
HE6p  208    IRPMEHCCCSVRIPCPSSPEELGKLLQCDLQDPIVCLADHPRGPPFSSSQSIPVVPRATVLSQVPKATSF
hU32p  58    IENSEEALTVHAPFPAAHPRSRSFPDPRGLYHFCLYWNRHAGRLHLLYGKRDFLLSDKASSLLCFQHQE
HE6p  277    AEPPDYSPVTHNVPSPIGEIQPLSPQPSAPIASSPAIDMPPQSETISSPMPQTHVSGTPPPVKASFSSP
hU32p 127    ESLAQGPPLLATSVTSWWSPQNISLPSAASFTFSFHSPPHTAAHNASVDMCELKRDLQLLSQFLKHPQK
HE6p  346    TVSLAPANVNTTSAPPVQTDIVNTSSISDLENQVLQMEKALSLGSLEPNLAGEMINQVSRLLLHSPPDMLA
hU32p 196    ASRRPSAAPASQQLQSLESKLTSVRFMGDMVSFEEDRINATVWKLQPTAGLQDLHIHSRQEEQSEIME
HE6p  415    PLAQRLLKVVDDIGLQLNFSNITISLTSPSLALAVIRVNASSFNTTTFVAQDPANLQVSLEETQAPENSI
hU32p 265    YSVLLPRTLFQRTKGRSGEAEKRLLLVDFSSQALFQDKNSSQV-LGEKVLGIVVQNTKVANLTEPVVLTI
HE6p  484    GTITLPSSLMNNLPAHDMELASRVQFNFEETPALFQDPSLENLSLISYVISSSVANLTVRNLIRNVTVLI
hU32p 333    FQHQLQPKN-VTLQCVFWVEDPTLSSPGHWSAGCE-TVRRETQTSCFCNHLTYFAVLMVSSVEVDAVH
HE6p  553    LKHINPSQDELIVRACVFW-DLGRNGGRGGWSDNGQSVKDRRLNETICTGSHLISFGVLLDLSRTSVLPA
hU32p 400    KH-YLSLLSYVGCVSALACLVTIAAYLCSRVPLPCRRKPRDYTIKVHMNLLLAVFLLDTSFLLSEPVA
HE6p  621    QMMALTFFITYIGGGLSSIFLSVTLVTYIAFEKIRRDYPSKILIQLCAALLLLNLVFLLDSWIALLYKMQ-
hU32p 468    LTGSEAGGRASAIFLHFSLLTCLSWMGLEGYNLYRLVVEVFGTYVPGVLKLSAMGWGFPIFLVTLVAL
HE6p  689    -----GLGISVAVFLHYFLLVSFTWMGLEAFHMYLALVKVFNTYIRKYILKFCIVGWGVPAVVVTIILT
hU32p 537    VDVDNYGPIILAVHRTPEGVIYPSMCWIRDSLVSYITNLGLFSLVFLFNAMLATMVVQILRLRPHTQKK
HE6p  753    ISPDNYGLGSYG---KFPNGSPDDFCWINNNAVFYITVVGYFCVIELLNVSMFIVVLVQLCRIKKKKQL
hU32p 606    WSHVLTL-LGLSLVLGLPWALIFFSFASGTFQLVV----LYLFSIITSFQGFLIFIWYWSMRLQARGGP
HE6p  819    GAQRKTS IQDLRSIAGLLTFLLGITWGFAFFAWGPVNVTFMYLFAIFNTLQGFFIFIFYCVAKENVRKQW
hU32p 670    SPLKSNSDCARLPISSGSTSSSRI
HE6p  888    RRYLCCGKLRLAENSDWSKTATNGLKKQTVNQGVSSSSNSTNSTTLLVNNDCSVHASGNGNA
HE6p  957    STERNGVSFSVQNGDVCLHDFTGKQHMFNEKEDSCNGKGRMALRRTSKRGSLHFIEQ
```

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00805

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07K 7/06, 14/705, 16/28, C12N 15/12, 5/10, C12P 21/02, A01K 67/027, G01N 33/68, C07H 21/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See below

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN, File Reg, "^MTPQSLLQTT/SQSP"
Gen Bank, Swiss Prot., EMBL, PIR: SEQ ID. No 1, SEQ ID. No 2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Biochemical and Biophysical Research Communications vol. 198 No. 1 (1994) Pages 328-334; MacNeil, Douglas J., et al. "Cloning and Expression of a Human Glucagon Receptor" Abstract, figure 1	18,19
X	DNA and Cell Biology vol. 16, No. 4 (1997) pages 379-389. Osterhoff, C et al "Cloning of a Human Epididymus-Specific mRNA, He6, Encoding an Novel Member of the Seven Transmembrane-Domain Receptor Superfamily" Abstract, figure 4, page 381 column 1	18,19

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
13 November 1998

Date of mailing of the international search report
17 NOV 1998

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00805

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Gene, vol 140 (1994) pages 203-209, Lok. S et al "The Human Glucagon receptor encoding gene: structure, cDNA sequence and chromosomal localization" whole document, especially page 203 column 2, page 204 column 2 part (c), figure 1.	18,19
P,X	Biochimica et Biophysica Acta 1395 (1998) pages 301-308, Mayer, H et al. "Isolation, molecular characterization, and tissue-specific expression of a novel putative G protein-coupled receptor" Abstract; figure 2,; page 307 column 1, last paragraph.	18,19